Acupuncture for the Management of Cancer-Related Pain?

Authors

Carole A. Paley, PhD, M.Med.Sci, BSc [1,2]

Mark I. Johnson, PhD, BSc [1]

Affiliations

1. Centre for Pain Research, School of Clinical and Applied Sciences, Leeds Beckett University City Campus, Leeds LS1 3HE, United Kingdom e-mail: m.johnson@leedsbeckett.ac.uk

2. Research and Development Dept. Airedale NHS Foundation Trust, Skipton Road, Steeton, Keighley BD20 6TD, United Kingdom

Address for correspondence

Professor Mark I. Johnson

M.Johnson@Leedsbeckett.ac.uk

Journal: Pain Management

Article Type: Commentary

Running header: Acupuncture for cancer pain

FUNDING: No external funding or assistance was provided for writing this Editorial

ETHICAL APPROVAL: N/A

COMPETING INTERESTS: None

ACKNOWLEDGEMENTS: None

ACCESSING RESEARCH MATERIALS: Underlying materials related to this article can be accessed by contacting Dr Carole Paley

Keywords: Acupuncture, Cancer, Pain

Word count: 1873

Tables: 0

Figures: 1

Treatment of cancer-related pain

The treatment and relief of cancer pain represents a challenge to healthcare professionals. Up to 70% of patients with advanced stage cancer suffer from pain for which they receive inadequate pain relief and this in turn leads to impaired physical and psychological well-being, resulting in a poorer quality of life [1]. Pain experienced by patients with cancer may be due to pre-existing pathologies, progression of the disease, tumour growth, bone metastases or the treatment of cancer itself. Strong opioids are commonly used to treat cancer-related pain but they may cause undesirable side-effects such as sedation, constipation and nausea which further reduces the quality of life [2]. Consequently, healthcare professionals and patients have sought non-pharmacological treatments to use on their own or in combination with drug therapies to alleviate cancer-related pain.

Western medical acupuncture is the insertion of fine needles into specific points on the body (acupuncture points) to stimulate nerves in skin and muscles using a conventional medical diagnostic approach and a course of treatment consisting of up to 10 sessions each lasting 20-60 minutes [3]. In the U.K. the National Institute for Health and Care Excellence (NICE) recommends a course of up to 10 sessions of acupuncture for the prophylactic treatment of chronic tension-type headache and migraine with or without aura [4] but does not recommend acupuncture for painful conditions such as osteoarthritis, low back pain or stable angina. In 2009, NICE had recommended that acupuncture should be used as a first line treatment for the early management of persistent non-specific low back pain with or without sciatica [5] but this recommendation was reversed in an update of the guidelines in 2016 [6]. A systematic review of current evidence on non-pharmacologic therapies for acute or chronic non-radicular or radicular low back pain for an American College of Physicians Clinical Practice Guideline concluded there was evidence that acupuncture was modestly effective for acute low back pain, although the strength of evidence was low [7].

Over one decade ago it was claimed that acupuncture had a role in the management of cancer-related pain [8-10] and guidelines for providing acupuncture treatment for cancer patients were published in the U.K. [11]. In 2004, NICE published guidance on improving supportive and palliative care for adults with cancer which recognised that a large proportion of patients with cancer used complementary therapies, including acupuncture, to manage distress, anxiety, pain and nausea associated with their condition [12]. NICE recommended that commissioners should be responsible for decisions about funding local provision for complementary therapy services taking account of the views of patients and health and social care professionals. NICE did not make recommendations

about individual complementary therapies but noted that there was weak evidence to support the use of acupuncture to alleviate pain and chemotherapy-related nausea and vomiting. Cancer Research UK includes a section on their website describing the uses of acupuncture for cancer-related symptoms, giving a review of past and current research and the findings of several systematic reviews (http://www.cancerresearchuk.org/about-cancer/cancers-in-general/treatment/complementary-alternative/therapies/acupuncture). The aim of this Commentary is to outline the current status of evidence for the use of acupuncture for cancer-related pain.

Evidence for acupuncture and alleviation of chronic non-cancer pain

There have been many systematic reviews of acupuncture for a wide variety of painful conditions. A systematic review of 35 systematic reviews in 2006 found that systematic reviews tend to overstate the effectiveness of acupuncture due to the inclusion of randomised controlled trials with small sample sizes and weak methodological quality leading to high risk of bias [13]. A meta-analyses of individual data from 17,922 patients (29 RCTs) published in 2012 attempted to overcome this problem and found that acupuncture was superior to placebo acupuncture and no-acupuncture controls for back and neck pain, osteoarthritis, chronic headache, and shoulder pain, and that the results were robust to sensitivity analyses assessing various potential sources of bias [14], although different characteristics of acupuncture did not appear affect pain outcomes [15]. In 2016, a meta-analysis of 20 trials (6376 patients) found that 50% of the benefit of acupuncture persisted at 12 months when compared with sham suggesting that treatment effects persist [16].

Evidence for acupuncture and alleviation of cancer-related pain

There is less research on the efficacy of acupuncture for cancer-related pain. In 2013, Towler et al. [17] reviewed 17 reviews and although there was evidence that acupuncture relieved cancer-related pain, nausea, vomiting, fatigue, hot flushes, xerostomia, dyspnoea and anxiety, variation in the design and methodological quality of trials made meaningful conclusions about effectiveness impossible. In 2014, a systematic review of 33 RCTs on acupuncture for the management of a variety of cancer-related symptoms included 6 RCTs (476 participants) on cancer-related pain, all of which found significant differences in at least one primary outcome compared with the control groups [18]. In 2015, Wu et al. [19] overviewed evidence from 23 systematic reviews and found conflicting evidence for the treatment of cancer-related pain with acupuncture, although it was noted that no serious adverse effects reported in any study. Chien et al. [20] published a systematic review and found that three of five RCTs reported that acupuncture was beneficial for treating aromatase

inhibitor-related joint-related pain and stiffness in breast cancer when compared with sham, although meta-analysis failed to detect statistically significant reductions (n=82 participants). We published a Cochrane systematic review of acupuncture for cancer pain in adults that included five RCTs (285 participants) investigating unspecified cancer, chronic neuropathic pain related to cancer, and pain associated with pancreatic cancer, ovarian cancer or stomach carcinoma. We concluded that there was insufficient evidence to judge whether acupuncture was effective because of high risk of bias from inadequate sample sizes [21]. Since then systematic reviews evaluating the efficacy of acupuncture for cancer-related pain have been positive but not definitive.

A meta-analysis by Lau et al. [22] suggested that acupuncture and related therapies reduced pain associated with liver or gastric cancer, with adverse events being infrequent and mild although only 175 participants (2 studies) were included in the analysis. Hu et al. [23] conducted a larger systematic review of 20 RCTs (1,639 participants). Meta-analysis of 845 participants (11 RCTs) found that acupuncture combined with conventional drug therapy was more effective at relieving cancer-related pain than drug therapy on its own, although acupuncture on its own was not superior to drug therapy (892 participants, 9 RCTs). Generally, the methodological quality of RCTs was low. Kim et al., [24] published a systematic review of seven RCTs (540 participants) and found low quality evidence for the efficacy and safety of acupuncture for recovery after surgery in colorectal cancer patients compared with compared with usual/routine care, sham interventions or active treatments. In 2017 Chui et al. [25] published a systematic review of 29 RCTs and estimated the overall effect size for acupuncture on cancer-related pain was -0.63 to -0.26 (95% confidence interval) with sub analyses providing evidence that acupuncture relieved pain associated with malignancy or surgery but not chemotherapy, radiotherapy or hormone therapy. However, most of the included studies were at high risk of methodological bias due to inconsistency and variation in treatment protocols and small sample sizes

Making sense of evidence from clinical research

At present, evidence from clinical research to support the use of acupuncture to alleviate cancer-related pain is promising but not definitive because there are too few RCTs and those that exist have inadequate sample sizes and methodological shortcomings. The findings of individual RCTs with small samples are unlikely to be correct and can bias the findings of meta-analyses towards overestimation of treatment effects [26, 27]. Estimates of efficacy when pooling data from multiple RCTs are less likely to be credible if there are fewer than 500 participants per treatment arm [26]. Meta-analyses of acupuncture and chronic pain meet this criterion. The size of the sample for

pooling data on acupuncture for cancer-related pain is growing with the publication of new RCTs and the meta-analysis of 845 participants by Hu et al. [23] that provides tentative evidence that acupuncture may be beneficial if combined with conventional drug therapy is noteworthy. Nevertheless, the methodological quality of RCTs remains a concern leading to a high risk of bias. There is little consensus on what constitutes a clinically important difference in pain outcomes and investigators in acupuncture trials often express pain data as means. Studies of analgesic medication suggest that few patients experience moderate improvement of pain but rather some patients experience substantial reductions in pain whereas others experience minimal improvement. Thus, analysing mean data may be misleading because participants that respond very well to the intervention may be hidden within a small between-group effect size [28]. Responder analyses using dichotomous data better reflects the clinical importance of change in pain associated with interventions by calculating the number of patients achieving ≥ 30% (moderately important change) and ≥ 50% (substantially important change) in line with the Measurement and Pain Assessment in Clinical Trials (IMMPACT) definitions for interpreting the clinical importance in change in outcome measures compared with baseline [29, 30].

Another challenge facing investigators and reviewers is how to manage inconsistency of acupuncture treatment protocols used in RCTs. There is variability in the selection of points, number of needles, depth of insertion, manipulation and stimulation of needles, the presence or otherwise of needle sensation ('de qi') and in the number and duration of treatment sessions in RCTs [31]. Ezzo et al. recommended that the minimum effective dose for acupuncture when used to alleviate pain should be at least one treatment session of more than 20 minutes each week using at least 4 points [32]. NICE recommends a course of up to 10 sessions of acupuncture for the prophylactic treatment of chronic tension-type headache and migraine [4].

Can we justify using acupuncture for cancer-related pain?

Patients ask for acupuncture and many practitioners consider acupuncture to be a viable treatment option for the relief of cancer-related pain, particularly in the palliative care setting where there might be limited treatment options [17, 18]. Evaluating clinical evidence on acupuncture is challenging and can present a confusing picture for the health care professional. You can be certain of uncertainty when evaluating clinical research on acupuncture to alleviate chronic pain [33]. To date, clinical evidence to support benefits for cancer-related pain is promising but not definitive. Acupuncture is a complex treatment intervention and optimum treatment characteristics only partially known, so acupuncture regimens are tailed according to individual need often based on the

experience of the practitioner and wide variability in response between individuals is common. It is not possible to predict with any degree of confidence whether a patient will respond, as is the case with many pain relieving interventions. Evidence from biomedical sciences suggests that acupuncture may elicit anti-nociceptive effects via peripheral and central mechanisms that would provide a scientific rationale for the relief of pain associated with metastatic cancer, including cancer-induced-bone pain and cancer breakthrough pain [34, 35] (Figure 1). Evidence-based medicine is an amalgamation of evidence supporting a plausible scientific rationale and evidence from clinical research informed by clinical experience. Acupuncture is relatively inexpensive, safe and readily accessible and there is no doubt that some patients benefit from treatment. Therefore, acupuncture should continue to be considered as a treatment option in addition to standard regimes until strong evidence from clinical research concludes otherwise.

REFERENCES

1. Van Den Beuken-Van Everdingen MHJ, De Rijke JM, Kessels AG, Schouten HC, Van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann. Oncol.* 18(9), 1437-1449 (2007).
2. Portenoy RK. Treatment of cancer pain. *Lancet* 377(9784), 2236-2247 (2011).
3. White A. Western medical acupuncture: a definition. *Acupunct. Med.* 27(1), 33-35 (2009).
4. National Institute for Health and Clinical Excellence (NICE). Headaches in over 12s: diagnosis and management. Clinical Guideline [CG150]. 3-30 (2015).
5. National Institute for Health and Clinical Excellence (NICE). Early management of persistent non-specific low back pain. Clinical Guideline [CG 88]. 1-25 (2009).
6. National Institute for Health and Clinical Excellence (NICE). Low back pain and sciatica in over 16s: assessment and management. Clinical Guideline [NG59]. 1-18 (2016).
7. Chou R, Deyo R, Friedly J *et al.* Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann. Intern. Med.* (2017).
8. Filshie J. Acupuncture for Malignant Pain. *Acupunct. Med.* 8(2), 38-39 (1990).
9. Filshie J, Hester J. Guidelines for providing acupuncture treatment for cancer patients - a peer-reviewed sample policy document. *Acupuct. Med.* 24(4), 172-182 (2006).
10. Filshie J, Rubino C. Promising results of auriculoacupuncture in the treatment of cancer pain. *Focus on Alternative & Complementary Therapies* 9(2), 132-133 (2004).
11. Alimi D, Rubino C, Pichard-Leandri E, Fermand-Brule S, Dubreuil-Lemaire ML, Hill C. Analgesic effect of auricular acupuncture for cancer pain: a randomized, blinded, controlled trial. *J. Clin. Oncol.* 21(22), 4120-4126 (2003).
12. National Institute for Health and Clinical Excellence (NICE). Improving supportive and palliative care for adults with cancer. Cancer Service Guideline [CSG4]. 1-204 (2004).
13. Derry CJ, Derry S, McQuay HJ, Moore RA. Systematic review of systematic reviews of acupuncture published 1996-2005. *Clin. Med.* 6(4), 381-386 (2006).
14. Vickers AJ, Cronin AM, Maschino AC *et al.* Acupuncture for chronic pain: individual patient data meta-analysis. *Arch. Intern. Med.* 172(19), 1444-1453 (2012).
15. MacPherson H, Maschino AC, Lewith G *et al.* Characteristics of acupuncture treatment associated with outcome: an individual patient meta-analysis of 17,922 patients with chronic pain in randomised controlled trials. *PLoS One* 8(10), e77438 (2013).

16. MacPherson H, Vertosick EA, Foster NE *et al*. The persistence of the effects of acupuncture after a course of treatment: a meta-analysis of patients with chronic pain. *Pain* (2016).
17. Towler P, Molassiotis A, Brearley SG. What is the evidence for the use of acupuncture as an intervention for symptom management in cancer supportive and palliative care: an integrative overview of reviews. *Supp. Care Cancer* 21(10), 2913-2923 (2013).
18. Lian WL, Pan MQ, Zhou DH, Zhang ZJ. Effectiveness of acupuncture for palliative care in cancer patients: a systematic review. *Chin. J. Integr. Med.* 20(2), 136-147 (2014).
19. Wu X, Chung VC, Hui EP *et al*. Effectiveness of acupuncture and related therapies for palliative care of cancer: overview of systematic reviews. *Sci. Rep.* 5 16776 (2015).
20. Chien TJ, Liu CY, Chang YF, Fang CJ, Hsu CH. Acupuncture for treating aromatase inhibitor-related arthralgia in breast cancer: a systematic review and meta-analysis. *J. Altern. Complem. Med.* 21(5), 251-260 (2015).
21. Paley CA, Johnson MI, Tashani OA, Bagnall AM. Acupuncture for cancer pain in adults. *Cochrane Database Syst. Rev.* (10), CD007753 (2015).
22. Lau CH, Wu X, Chung VC *et al*. Acupuncture and Related Therapies for Symptom Management in Palliative Cancer Care: Systematic Review and Meta-Analysis. *Medicine (Baltimore)* 95(9), e2901 (2016).
23. Hu C, Zhang H, Wu W *et al*. Acupuncture for Pain Management in Cancer: A Systematic Review and Meta-Analysis. *Evid. Based Complement. Alternat. Med.* 2016 1720239 (2016).
24. Kim KH, Kim DH, Kim HY, Son GM. Acupuncture for recovery after surgery in patients undergoing colorectal cancer resection: a systematic review and meta-analysis. *Acupunct. Med.* 34(4), 248-256 (2016).
25. Chiu HY, Hsieh YJ, Tsai PS. Systematic review and meta-analysis of acupuncture to reduce cancer-related pain. *Eur. J. Cancer Care* 26(2), (2017).
26. Moore RA, Gavaghan D, Tramer MR, Collins SL, Mcquay HJ. Size is everything--large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 78(3), 209-216 (1998).
27. Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ* 346 f2304 (2013).
28. Moore RA, Derry S, Wiffen PJ. Challenges in design and interpretation of chronic pain trials. *Br. J. Anaesth.* 111(1), 38-45 (2013).
29. Moore RA, Edwards JE, McQuay HJ. Acute pain: individual patient meta-analysis shows the impact of different ways of analysing and presenting results. *Pain* 116(3), 322-331 (2005).
30. Dworkin RH, Turk DC, McDermott MP *et al*. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain* (2009).
31. White A, Cummings M, Barlas P *et al*. Defining an adequate dose of acupuncture using a neurophysiological approach--a narrative review of the literature. *Acupunct. Med.* 26(2), 111-120 (2008).
32. Ezzo J, Berman B, Hadhazy VA, Jadad AR, Lao L, Singh BB. Is acupuncture effective for the treatment of chronic pain? A systematic review. *Pain* 86(3), 217-225 (2000).
33. Johnson MI. The clinical effectiveness of acupuncture for pain relief - you can be certain of uncertainty. *Acupunct. Med.* 24(2), 71-79 (2006).
34. Paley CA, Bennett MI, Johnson MI. Acupuncture for cancer-induced bone pain? *Evid Based Complement Alternat. Med.* 2011 671043 (2011).
35. Paley CA, Johnson MI, Bennett MI. Acupuncture: a treatment for breakthrough pain in cancer? *BMJ Support. Palliat. Care* 1(3), 335-338 (2011).

FIGURE LEGEND

Figure 1

Potential mechanisms of analgesic action of acupuncture.